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Dated 23 January 2003

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1/77

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**The Patent Office**

Cardiff Road
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Gwent NP9 1RH

1. Your reference — 100649

2. Patent application number *(The Patent Office will fill in this part)* — **0204392.5** — 26 FEB 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 7822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

PHARMACEUTICAL COMPOUND

5. Name of your agent *(if you have one)*

Brian Steele Tait

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 7726276002

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| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body.*
*See note (d))*

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| Description | 27 |
| Claim(s) | 03 |
| Abstract | |
| Drawing(s) | 05 + 5 |

10. If you are also filing any of the following, state how many against each item.

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| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application.

Signature J.M. Marshall Date

Authorised Signatory 25/02/2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Joanne M. Marshall - 01625 - 516485

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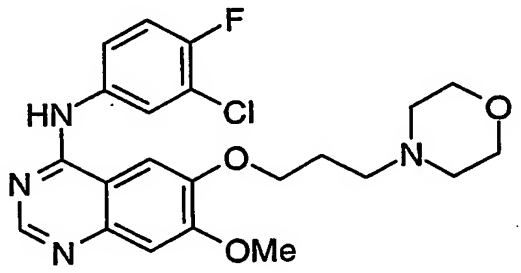
# PHARMACEUTICAL COMPOUND

The present invention relates to particular crystalline forms of a pharmaceutical compound, to processes for their preparation, to their use in the purification of that pharmaceutical compound, to pharmaceutical compositions comprising them and to their use in therapy.

International Patent Application WO 96/33980 discloses within Example 1 the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline. That compound is an inhibitor of the epidermal growth factor receptor (EGFR) family of tyrosine kinase enzymes such as erbB1 and possesses anti-proliferative activity such as anti-cancer activity and, accordingly, is useful in methods of treatment of proliferative disease such as cancer in the human or animal body.

That compound has the structure of the Formula I




I

and is now known as Iressa (registered trade mark) and gefitinib (Unites States Adopted Name) and by way of the code number ZD1839 and Chemical Abstracts Registry Number 184475-35-2.

The subject matter of Example 1 of International Patent Application WO 96/33980 discloses the preparation of the compound of the Formula I which, after purification by column chromatography on silica using a 4:1 mixture of ethyl acetate and methanol as eluent and recrystallisation from toluene, is stated to have m.p. 119-120°C. The subject matter of Example 10 of that patent application discloses an alternative synthetic route to the compound of the Formula I that involves purification by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent and recrystallisation from toluene. There is no specific disclosure in either of Examples 1 and 10 of International Patent Application WO 96/33980 whether the compound of the Formula I is crystalline or amorphous. Furthermore, there is no specific disclosure in those examples whether the compound may exist in a solvated form.

It is stated in International Patent Application WO 96/33980 that the quinazoline derivatives disclosed therein can exist in solvated as well as unsolvated forms such as, for example, hydrated forms and that the invention therein encompasses all such solvated forms which possess anti-proliferative activity. However, no particular hydrated forms are disclosed and no particular solvates are disclosed.

We have now found that certain forms of the compound of Formula I including certain solvates thereof are crystalline materials that possess advantageous properties.

A particular crystalline form of a compound may have physical properties that differ from those of any other crystalline or amorphous form and such properties may influence markedly the chemical and pharmaceutical processing of the compound, particularly when the compound is prepared or used on a commercial scale. For example, each crystal form of a compound may show differences in physical properties such as crystalline size and shape, melting point, density, hygroscopicity and stability. Such differences may alter the mechanical handling properties of the compound (such as the flow characteristics of the solid material) and the compression characteristics of the compound. Different crystalline forms of a compound may have different thermodynamic stabilities. In general, the more stable form, for example the more stable polymorphic form, is the more suitable physical form for formulation and processing on a commercial scale.

For example, problems could arise in the processing of a less stable form, for example a less stable polymorph. Compression forces such as those used in tabletting processes could convert some of a less stable form into a more stable form resulting in growth of crystals of the more stable form in the formulated product. This could be undersirable since any such crystallisation process could disrupt the integrity of the tablet resulting in a friable tablet of decreased tablet strength. In addition, if a variable mixture of two such forms were to be present, the dissolution rate and bioavailability of the active compound(s) could be variable as, for example, each form could have a different particle size. It is well known that particle size can affect the dissolution rate and bioavailabilty of a pharmaceutically-active compound. The quality of the product could therefore be affected undesirably.

Furthermore it is preferred that pharmaceutical compounds in the form of capsules or tablets are prepared using the most stable form, for example the most stable polymorph, and not a metastable phase or mixture of forms as there is a requirement to demonstrate to the appropriate regulatory authorities that the composition of the compound is controlled and stable. If a thermodynamically less stable form, for example a less stable polymorph, were

present alone or in admixture with a thermodynamically more stable form in a tablet, it would be very difficult to control the composition of the tablet, for example the polymorphic composition of the tablet, since the quantity of the more thermodynamically stable form could tend to increase on storage.

Accordingly, these factors may have an impact on solid phase, tablet or capsule formulations of the compound and on suspension formulations thereof.

A study of the properties of the compound of the Formula I has been performed to discover whether polymorphism and/or solvate formation is possible. A wide range of recrystallisation solvents of various polarities was investigated. From most of these solvents, only a single non-solvated, crystalline form of the compound of the Formula I was obtained which is designated hereinafter as Form 1 ZD1839 polymorph. Two solvates were also identified as of interest. The first solvate occurred in the presence of methanol and this is designated hereinafter as the Form 2 ZD1839 MeOH solvate and the second solvate occurred with dimethyl sulphoxide and this is designated hereinafter as the Form 3 ZD1839 DMSO solvate.

In particular, it has now been found that Form 3 ZD1839 DMSO solvate is crystalline and that, surprisingly, that form has advantageous properties.

Further, we have discovered that Form 3 ZD1839 DMSO solvate is unusual in that it possesses a crystalline physical form that is easily isolated and is also very stable. Moreover, this solvate may readily be prepared on a commercial scale at a high level of purity and in high yield. In addition this solvate may readily be converted into the compound of Formula I, in particular into the compound of Formula I in the form of Form 1 ZD1839 polymorph. Overall, the inclusion of the steps of DMSO solvate preparation, purification thereof and conversion back to the compound of Formula I is beneficial in terms of yield and purity of the compound of Formula I.

According to one aspect of the present invention there is provided a crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate.

According to a further aspect of the present invention there is provided a crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate and substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph.

When it is stated that the present invention relates to a crystalline form of the compound of the Formula I, the degree of crystallinity as determined by X-ray powder diffraction data is conveniently greater than about 60%, more conveniently greater than about 80%, preferably greater than about 90% and more preferably greater than about 95%. Most preferably, the degree of crystallinity as determined by X-ray powder diffraction data is greater than about 98%.

When it is stated that the present invention relates to Form 3 ZD1839 DMSO solvate, the molar ratio of ZD1839 to dimethyl sulphoxide solvent molecule is in the range 3:1 to 1:3, preferably in the range 2:1 to 1:2, more preferably about 1 equivalent of ZD1839 to about 1 equivalent of DMSO.

When it is stated that the present invention relates to a crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate, this means that at least 80% of the compound of the Formula I is in the form of Form 3 ZD1839 DMSO solvate. Preferably at least 90% and, in particular, at least 95% of the compound of the Formula I is in the form of Form 3 ZD1839 DMSO solvate. More preferably at least 98% of the compound of the Formula I is in the form of Form 3 ZD1839 DMSO solvate.

When it is stated that the invention relates to Form 3 ZD1839 DMSO solvate substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph, this means that at least 80% of the compound of the Formula I is in the form of Form 3 ZD1839 DMSO solvate and less than 20% of the compound of the Formula I is in the form of any other ZD1839 solvate or any Form 1 ZD1839 polymorph. Preferably at least 90% and, in particular, at least 95% of the compound of the Formula I is in the form of Form 3 ZD1839 DMSO solvate.

Further, we have discovered that Form 2 ZD1839 MeOH solvate also possesses a crystalline physical form that is easily isolated and it is of sufficient stability readily to be prepared on a commercial scale at a high level of purity and in high yield. In addition this solvate may be converted into the compound of Formula I.

According to a further aspect of the present invention there is provided a crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate.

According to a further aspect of the present invention there is provided a crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate and substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph.

When it is stated that this aspect of the present invention relates to a crystalline form of the compound of the Formula I, the degree of crystallinity as determined by X-ray powder diffraction data is conveniently greater than about 60%, more conveniently greater than about 70%, preferably greater than about 80% and more preferably greater than about 90%. Most preferably, the degree of crystallinity as determined by X-ray powder diffraction data is greater than about 95%.

When it is stated that the present invention relates to Form 2 ZD1839 MeOH solvate, the molar ratio of ZD1839 to methanol solvent molecule is in the range 6:1 to 1:3, preferably in the range 4:1 to 1:2, more preferably about 2 equivalents of ZD1839 to about 1 equivalent of methanol, *i.e.* the material can be approximately a hemi-solvate.

When it is stated that the present invention relates to a crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate, this means that at least 80% of the compound of the Formula I is in the form of Form 2 ZD1839 MeOH solvate. Preferably at least 90% and, in particular, at least 95% of the compound of the Formula I is in the form of Form 2 ZD1839 MeOH solvate. More preferably at least 98% of the compound of the Formula I is in the form of Form 2 ZD1839 MeOH solvate.

When it is stated that the invention relates to Form 2 ZD1839 MeOH solvate substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph, this means that at least 80% of the compound of the Formula I is in the form of Form 2 ZD1839 MeOH solvate and less than 20% of the compound of the Formula I is in the form of any other ZD1839 solvate or any Form 1 ZD1839 polymorph. Preferably at least 90% and, in particular, at least 95% of the compound of the Formula I is in the form of Form 2 ZD1839 MeOH solvate.

Certain other solvates of the compound of Formula I may be obtained but these do not possess crystalline physical forms that are both easily isolated and stable. For example, when the compound of Formula I was allowed to crystallise by the slow evaporation of a solvent system comprising a mixture of isopropanol and water, the crystalline solid obtained comprised an isopropanolate solvate that also carried two equivalents of water. However, for example, when the compound of Formula I was recrystallised in a solvent system comprising

a mixture of isopropanol and water, the crystalline solid obtained comprised not only Form 1 ZD1839 polymorph but also a further material which is believed to be a metastable anhydrate ZD1839 polymorphic form.

In contrast, from many solvents only a single non-solvated, crystalline form of the compound of the Formula I was obtained which is designated as Form 1 ZD1839 polymorph. We have discovered that Form 1 ZD1839 polymorph possesses a crystalline physical form that is easily isolated and is also highly stable such that this polymorph may readily be prepared on a commercial scale at a high level of purity and in high yield. The compound of the Formula I can thereby be obtained substantially in the form of Form 1 ZD1839 polymorph, preferably substantially free of any other polymorphic form of ZD1839 or of any ZD1839 solvate.

Form 1 ZD1839 polymorph has a melting point in the range of about 194°C to 198°C. It was not disclosed in International Patent Application WO 96/33980 that the compound of the Formula I could exist in a polymorphic form of m.p. about 195°C, nor was a process disclosed for preparing that polymorph substantially free of any other polymorphic form of ZD1839 or of any ZD1839 solvate. It was disclosed in International Patent Application WO 96/33980 that the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, now known by way of the code number ZD1839, had m.p. 119-120°C. It is believed that the material obtained at that time may have been the metastable anhydrate polymorphic form of ZD1839.

When it is stated that a crystalline form of the compound of the Formula I in the form of Form 1 ZD1839 polymorph may be obtained, the degree of crystallinity as determined by X-ray powder diffraction data is conveniently greater than about 60%, more conveniently greater than about 70%, preferably greater than about 80% and more preferably greater than about 90%. Most preferably, the degree of crystallinity as determined by X-ray powder diffraction data is greater than about 95%.

When it is stated that a crystalline form of the compound of the Formula I may be obtained that is substantially in the form of Form 1 ZD1839 polymorph, this means that at least 80% of the compound of the Formula I is in the form of Form 1 ZD1839 polymorph. Preferably at least 90% and, in particular, at least 95% of the compound of the Formula I is in the form of Form 1 ZD1839 polymorph. More preferably at least 98% of the compound of the Formula I is in the form of Form 1 ZD1839 polymorph.

When it is stated that Form 1 ZD1839 polymorph may be obtained substantially free of any other polymorphic form of ZD1839 or of any ZD1839 solvate, this means that at least 80% of the compound of the Formula I is in the form of Form 1 ZD1839 polymorph. Preferably at least 90% and, in particular, at least 95% of the compound of the Formula I is in the form of Form 1 ZD1839 polymorph.

Samples of the particular crystalline forms of the compound of the Formula I were analysed using a combination of X-Ray Powder Diffraction (hereinafter XRPD) analysis, Differential Scanning Calorimetry (hereinafter DSC), Thermal Gravimetric Analysis (hereinafter TGA), Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy and/or Near Infrared (NIR) spectroscopy.

X-ray diffraction data were obtained using Siemens D5000 equipment, the use of which is described in more detail hereinafter. It will be appreciated that different equipment and/or conditions may result in slightly different data being generated. Hence the figures quoted are not to be taken as absolute values. The compound of Formula I in the form of Form 1 ZD1839 polymorph has the X-ray diffraction pattern shown in Figure 1 hereinafter having characterising peaks [on the 2 theta ($\theta$) scale] at about 7.0, 11.2, 15.8, 19.3, 24.0 (largest peak) and 26.3°.

Melting points and TGA were determined using Perkin Elmer Pyris 1 DSC/TGA equipment, the use of which is described in more detail hereinafter. It will be appreciated that alternative readings of melting point may be given by other types of equipment or by using conditions different to those described hereinafter. Hence the figures quoted are not to be taken as absolute values. The DSC thermogram and TGA for Form 1 ZD1839 polymorph is shown in Figure 2 hereinafter. This polymorph has a melting point in the range of about 194°C to 198°C. More particularly, the melting point is in the range of about 194.5°C to 196.5°C. Most particularly, the melting point is in the range of about 195°C to 196°C.

DRIFT spectroscopy data were obtained on a Nicolet 20SXC spectrometer, the use of which is described in more detail hereinafter. It will be appreciated that slightly different data may be generated if different equipment and/or conditions of sample preparation are used. Hence the figures quoted are not to be taken as absolute values. The DRIFT spectroscopy trace for Form 1 ZD1839 polymorph is shown in Figure 3 hereinafter with distinguishing peaks at about 3400, 1630, 1525, 1245 and 840$cm^{-1}$.

In addition, there is the potential for Form 1 ZD1839 polymorph to be characterised and/or distinguished from other physical forms by other techniques for example using NIR spectroscopy or solid state nuclear magnetic resonance spectroscopy.

In addition, the crystal structure of Form 1 ZD1839 polymorph was characterised by single-crystal X-ray analysis as described in more detail hereinafter. This polymorph crystallises in the triclinic space group P(-1) with two ZD1839 molecules in the unit-cell and the unit-cell dimensions are: $a = 8.876(1)$, $b = 9.692(1)$, $c = 12.543(1)$ Å, $\alpha = 93.51(1)$, $\beta = 97.36$, $\gamma = 101.70(1)°$ and $V = 1043.6(2)$ Å$^3$. Other data are shown in Tables A:1 and A:2 hereinafter within Example 5.

The compound of Formula I in the form of the metastable anhydrate ZD1839 polymorph when characterised by a DSC thermogram shows an initial exothermic event associated with conversion from the metastable form to Form 1 ZD1839 polymorph which, as disclosed hereinbefore, has an endothermic event corresponding to a melting point in the range of about 194°C to 198°C.

The compound of Formula I in the form of Form 2 ZD1839 MeOH solvate has the X-ray powder diffraction pattern shown in Figure 4 hereinafter having characterising peaks [on the 2 theta (θ) scale] at about 6.5 (largest peak), 10.0 and 13.2°.

The DSC thermogram and TGA for Form 2 ZD1839 MeOH solvate is shown in Figure 5 hereinafter. The trace shows an initial endotherm at approximately 130°C and a second endotherm at approximately 196°C. The second endotherm corresponds to that from the DSC thermogram from Form 1 ZD1839 polymorph and indicates that desolvation and a conversion to Form 1 ZD1839 polymorph has occurred on heating. The TGA shows a solvent loss of approximately 3% by weight at approximately 130°C. Thus Form 2 ZD1839 MeOH solvate has a desolvation point in the range of about 110°C to 140°C. More particularly, the desolvation point is in the range of about 125°C to 138°C.

The DRIFT spectroscopy trace for Form 2 ZD1839 MeOH solvate is shown in Figure 6 hereinafter with distinguishing peaks at about 3380, 1650, 1530, 1450, 1235, 870 and 570cm$^{-1}$.

The compound of Formula I in the form of Form 3 ZD1839 DMSO solvate has the X-ray powder diffraction pattern shown in Figure 7 hereinafter having characterising peaks [on the 2 theta (θ) scale] at about 8.9, 17.8, 22.6 (largest peak) and 23.2°.

The DSC thermogram and TGA for Form 3 ZD1839 DMSO solvate is shown in Figure 8 hereinafter. The TGA shows a solvent loss of approximately 14% by weight over a temperature range of approximately 80 to 105°C. The DSC trace shows an endotherm at approximately 130°C. Thus Form 3 ZD1839 DMSO solvate has a desolvation point in the range of about 125°C to 135°C. More particularly, the desolvation point is in the range of about 127°C to 132°C. Most particularly, the desolvation point is about 130°C.

The DRIFT spectroscopy trace for Form 3 ZD1839 DMSO solvate is shown in Figure 9 hereinafter with distinguishing peaks at about 1640, 1520, 1450, 880 and 560cm$^{-1}$.

The following particular crystalline forms of the compound of the Formula I are disclosed herein :-

(i) Form 3 ZD1839 DMSO solvate;

(ii) Form 2 ZD1839 MeOH solvate; and

(iii) Form 1 ZD1839 polymorph.

Each of these entities possesses the same pharmacological properties as those disclosed in International Patent Application WO 96/33980 for compounds such as 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, in particular anti-proliferative activity such as anti-cancer activity. These solvate and polymorph entities are described collectively hereinafter as 'the active substance of the invention'.

In order to use the active substance of the invention for the treatment of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore, according to another aspect of the invention there is provided a pharmaceutical composition which comprises the active substance of the invention and a pharmaceutically-acceptable diluent or carrier.

For example, the compositions of the invention may be in a form adapted for oral administration (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical administration (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for

rectal dosing).

A preferred method of administration is oral administration. The active substance of the invention is conveniently administered orally in the form of tablets. Specific examples of tablet formulations are described hereinafter.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Standard excipients include, for example, tablet diluents, dispersants, suspending and binding agents, structure formers, tablet lubricants, cryoprotectants and pH modifiers, such as, mannitol, sorbitol, lactose, glucose, sodium chloride, acacia, dextran, sucrose, maltose, gelatin, bovine serum albumin (BSA), glycine, mannose, ribose, polyvinylpyrrolidinone (PVP), cellulose derivatives such as microcrystalline cellulose, glutamine, inositol, potassium glutamate, magnesium stearate, sodium lauryl sulphate, talc, erythritol, serine and other amino acids, calcium carbonate, magnesium carbonate and other weak bases, and buffer agents, for example disodium hydrogen phosphate, calcium hydrogen phosphate and potassium citrate.

The amount of the active substance of the invention that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treatment and the particular route of administration. For example, a formulation intended for oral administration to humans will conveniently contain, for example, from 1 mg to 1 g of active substance compounded with an appropriate and convenient amount of excipient which may vary from about 5 to about 98 percent by weight of the total composition. Preferably the formulation will comprise, for example, from 50 mg to 750 mg of active substance. More preferably the formulation will comprise, for example, from 100 mg to 500 mg of active substance, especially about 250 mg of active substance.

In using the active substance of the invention for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.2 to 20 mg per kg body weight is received, given if required in divided doses. Preferably a daily dose in the range, for example, 0.5 to 15 mg per kg body weight is received. More preferably a daily dose in the range, for example, 1 to 10 mg per kg body weight is received.

The active substance of the invention shows an acceptable toxicity profile.

Further details of the uses of the compound of the Formula I and combinations containing the compound are disclosed in International Patent Application WO 96/33980.

The active substance of the invention possesses the same pharmacological properties as those disclosed in International Patent Application WO 96/33980 for the compound of the Formula I, in particular anti-proliferative activity such as anti-cancer activity. For example, the active substance of the invention is useful for the treatment of many common human cancers such as lung (including small cell lung cancer and non small cell lung cancer), breast, prostate, ovarian, colorectal, gastric, brain (including glioma and pituitary adenoma), head and neck, bladder, pancreas, oesophageal, stomach, renal, skin (including malignant melanoma), gynaecological (including cervical, endometrial, vaginal, vulval and uterine) and thyroid cancer and in the treatment of a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas. It is further expected that the active substance of the invention will be useful for the treatment of other diseases involving excessive cellular proliferation such as benign skin hyperplasia, for example psoriasis, and benign prostatic hypertrophy (BPH).

The pharmacological properties of the active substance of the invention may be assessed using, for example, one or more of the test procedures disclosed in International Patent Application WO 96/33980 or equivalent test procedures that are well within the compass of the man skilled in the art. Such test procedures from that patent application are incorporated herein by reference.

According to a further aspect of the present invention there is provided the active substance of the invention as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the active substance of the invention possesses anti-proliferative properties such as anti-cancer properties which are believed to arise from its EGF receptor (erbB1) tyrosine kinase inhibitory activity. Accordingly the active substance of the invention is expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by erbB1 receptor tyrosine kinases, *i.e.* the active substance of the invention may be used to produce an erbB1 receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the active substance of the invention provides a method for treating the proliferation of malignant cells characterised by inhibition of erbB1 receptor tyrosine kinases, i.e. the active substance of the invention may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of erbB1 receptor tyrosine kinase. Accordingly the active substance of the invention is expected to be useful in the treatment of psoriasis and/or cancer by providing an anti-proliferative effect, particularly in

the treatment of erbB1 receptor tyrosine kinase sensitive cancers such as lung, breast, prostate, ovarian, colorectal, gastric, brain, head and neck, bladder, pancreas, oesophageal, stomach, renal, skin, gynaecological and thyroid cancer.

Thus according to this aspect of the invention there is provided the use of the active substance of the invention as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of the active substance of the invention as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular proliferative disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range, for example, 0.5 to 15 mg per kg body weight is received. More preferably a daily dose in the range, for example, 1 to 10 mg per kg body weight is received. A unit dose in the range, for example, 1 to 1000 mg, conveniently 100 to 750 mg, more conveniently 200 to 600 mg, preferably about 250 mg is envisaged.

The active substance of the invention defined hereinbefore may be applied as a sole therapy or may involve, in addition to the active substance of the invention, conventional surgery and/or radiotherapy and/or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-cancer agents :-

(i) anti-invasion agents [for example metalloproteinase inhibitors such as MMP-2 (matrix-metalloproteinase-2) and MMP-9 (matrix-metalloproteinase-9) inhibitors, for example marimastat, and inhibitors of urokinase plasminogen activator receptor function];

(ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{o-fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin,

idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrazole, vorazole and exemestane) and inhibitors of

5α-reductase such as finasteride;

(iv) other inhibitors of growth factor function, for example growth factor antibodies, growth factor receptor antibodies such as C225, antibodies to components of the signal transduction cascade, for example antibodies to erbB2 such as trastuzumab, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example other inhibitors of the epidermal growth factor family such as N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033), for example inhibitors of the platelet-derived growth factor family, for example inhibitors of the protein product of the bcr-abl gene such as imatinib (STI571), for example inhibitors of the fibroblast growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856, WO 98/13354, WO 00/47212 and WO 01/32651 and those that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin); and

(vi) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib and rofecoxib.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agents within their approved dosage ranges.

According to this aspect of the invention there is provided a pharmaceutical product comprising the active substance of the invention as defined hereinbefore and an additional anti-cancer agent as defined hereinbefore for the conjoint treatment of cancer.

Processes for the preparation of the following particular crystalline forms of the compound of the Formula I are disclosed herein, namely processes :-

(i) for preparing Form 3 ZD1839 DMSO solvate;

(ii) for preparing Form 2 ZD1839 MeOH solvate; and

(iii) for preparing Form 1 ZD1839 polymorph.

We have discovered a process for preparing a crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate, preferably substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph. Such a process provides a further aspect of the present invention and comprises, for example, the steps of :-

(a) heating a mixture of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in dimethyl sulphoxide or a solvent mixture containing dimethyl sulphoxide and a co-solvent until dissolution has occurred;

(b) reducing the temperature of the solvent system to induce spontaneous nucleation;

(c) maintaining the mixture at a temperature below that at which nucleation has commenced; and

(d) isolating the crystalline solid so deposited.

The mixture may, for example, be heated to reflux until dissolution has occurred. Alternatively, the mixture may, for example, be heated to a temperature less than the reflux temperature of the solvent provided that dissolution of more or less all of the solid material has occurred. It will be appreciated that small quantities of insoluble material may be removed by filtration of the warmed mixture.

Suitable solvent mixtures include dimethyl sulphoxide and one or more co-solvents such as a polar protic solvent such as ethanol and isopropanol and/or a non-protic solvent such as tetrahydrofuran, acetone, ethyl acetate and N,N-dimethylformamide. For example, a suitable solvent is dimethyl sulphoxide. A further suitable solvent is a mixture of dimethylsulphoxide and ethyl acetate wherein the ratio by volume of ethyl acetate to dimethyl sulphoxide lies within the range 50:1 to 0.05:1, conveniently in the range 20:1 to 0.5:1, for

example 1 part of ethyl acetate and 1 part of dimethyl sulphoxide, 6 parts of ethyl acetate and 1 part of dimethyl sulphoxide or 13 parts of ethyl acetate and 1 part of dimethyl sulphoxide.

The solution of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in dimethyl sulphoxide or a solvent mixture containing dimethyl sulphoxide as one component may be removed from the heat source and allowed to cool to ambient temperature or it may be cooled further, for example to about 0°C in an bath of ice and water. Alternatively, the solution may be cooled at a controlled rate to about 0°C. A suitable cooling rate is, for example, about 10°C per hour.

The crystalline solid may be isolated by any conventional method, for example by filtration or centrifugation.

It will be appreciated by the man skilled in the art that the procedures described above may be varied using routine skill and knowledge. For example, provided that a crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate is obtained, any of the quantity of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline that is treated, the volume of the DMSO solvent, the nature and volume of any co-solvent, the ratio of the component solvents if a solvent mixture is employed and the temperatures of the dissolution and cooling phases may be varied.

In addition Form 3 ZD1839 DMSO solvate may readily be converted into the compound of Formula I, particularly into Form 1 ZD1839 polymorph. Overall, the inclusion of the steps of DMSO solvate preparation, purification thereof and conversion into Form 1 ZD1839 polymorph is beneficial in terms of the yield and purity of the Form 1 ZD1839 polymorph so obtained. Such a process for the preparation of the compound of Formula I substantially in the form of Form 1 ZD1839 polymorph provides a further aspect of the present invention and comprises, for example, the steps of :-

(a) washing Form 3 ZD1839 DMSO solvate with a solvent or solvent mixture substantially to remove dimethyl sulphoxide; and

(b) isolating the Form 1 ZD1839 polymorph so formed.

Suitable solvents include, for example, a polar protic solvent such as ethanol or isopropanol or a non-protic solvent such as tetrahydrofuran, acetone, ethyl acetate or N,N-dimethylformamide. Mixtures of such solvents may also be employed. Ethyl acetate is a

preferred solvent for this washing procedure. Conveniently the washing solvent may be warmed, for example to a temperature of about 30°C to 50°C.

The crystalline solid may be isolated by any conventional method, for example by filtration or centrifugation.

Conveniently, the compound of Formula I substantially in the form of Form 1 ZD1839 polymorph that is obtained from the washing step may be purified further by recrystallisation. For example, the washed solid may be warmed in a suitable solvent as defined hereinbefore until dissolution has occurred, the temperature of the solution may be reduced to induce spontaneous nucleation, the temperature of the solution may be maintained below that at which nucleation has commenced and the crystalline solid so deposited may be isolated.

We have also discovered a process for preparing a crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate, preferably substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph. Such a process provides a further aspect of the present invention and comprises, for example, the steps of :-

(a) heating a mixture of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in methanol or a solvent mixture containing methanol and a co-solvent until dissolution has occurred;

(b) reducing the temperature of the solvent system to induce spontaneous nucleation;

(c) maintaining the mixture at a temperature below that at which nucleation has commenced; and

(d) isolating the crystalline solid so deposited.

The mixture may, for example, be heated to reflux until dissolution has occurred. The mixture may then be removed from the heat source and allowed to cool to ambient temperature or it may be cooled further, for example to about 0°C in an bath of ice and water. Alternatively, the solution may be cooled at a controlled rate to about 0°C. A suitable cooling rate is, for example, about 10°C per hour.

Suitable solvent mixtures include methanol and one or more co-solvents such as weakly polar solvents, for example aromatic hydrocarbons such as toluene, halogeno-(1-6C)alkanes such as 1,2-dichloroethane and aliphatic di-(1-6C)alkyl ethers or (4-7C)cyclic ethers such as tetrahydrofuran, other polar protic solvent such as ethanol and

isopropanol, polar non-protic solvents such as aliphatic esters such as ethyl acetate, aliphatic (3-6C)ketones such as acetone and aliphatic amides such as N,N-dimethylformamide. For example, a suitable solvent is methanol. A further suitable solvent is a mixture of methanol and a co-solvent selected from toluene and ethyl acetate where, for example, the ratio by volume of co-solvent to methanol lies within the range 50:1 to 0.05:1, conveniently in the range 20:1 to 0.5:1.

The solution of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in methanol or a solvent mixture containing methanol as one component may be removed from the heat source and cooled as described hereinbefore for the preparation of Form 3 ZD1839 DMSO solvate.

The crystalline solid may be isolated by any conventional method, for example by filtration or centrifugation.

It will be appreciated by the man skilled in the art that the procedures described above may be varied using routine skill and knowledge. For example, provided that a crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate is obtained, any of the quantity of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline that is treated, the volume of the methanol solvent, the nature and volume of any co-solvent, the ratio of the component solvents if a solvent mixture is employed and the temperatures of the dissolution and cooling phases may be varied.

In addition Form 2 ZD1839 MeOH solvate may be converted into the compound of Formula I, particularly into Form 1 ZD1839 polymorph. Such a process for the preparation of the compound of Formula I in the form of Form 1 ZD1839 polymorph provides a further aspect of the present invention and comprises, for example, the steps of :-

(a) washing Form 2 ZD1839 MeOH solvate with a solvent or solvent mixture substantially to remove methanol; and

(b) isolating the Form 1 ZD1839 polymorph so formed.

Suitable solvents include, for example, a polar protic solvent such as ethanol or isopropanol or a non-protic solvent such as tetrahydrofuran, acetone, ethyl acetate or N,N-dimethylformamide. Mixtures of such solvents may also be employed. Ethyl acetate is a preferred solvent for this washing procedure. Conveniently the washing solvent may be warmed, for example to a temperature of about 30°C to 50°C.

The crystalline solid may be isolated by any conventional method, for example by filtration or centrifugation.

Conveniently, the compound of Formula I substantially in the form of Form 1 ZD1839 polymorph that is obtained from the washing step may be purified further by recrystallisation. For example, the washed solid may be warmed in a suitable solvent as defined hereinbefore until dissolution has occurred, the temperature of the solution may be reduced to induce spontaneous nucleation, the temperature of the solution may be maintained below that at which nucleation has commenced and the crystalline solid so deposited may be isolated.

In addition, Form 2 ZD1839 MeOH solvate may be converted into the compound of Formula I in the form of Form 1 ZD1839 polymorph by warming the compound, for example by heating the compound to a temperature of about 125°C to 150°C, more particularly to a temperature of more than about 135°C.

A process for preparing a crystalline form of the compound of the Formula I substantially in the form of Form 1 ZD1839 polymorph has also been obtained. Preferably, the crystalline form of the compound of the Formula I substantially in the form of Form 1 ZD1839 polymorph is obtained substantially free of any other polymorphic form of ZD1839 or of any ZD1839 solvate. Such a process comprises, for example, the steps of :-

(a) dissolving the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in a solvent system in which solvate formation is repressed;

(b) reducing the temperature of the solvent system to induce spontaneous nucleation;

(c) maintaining the mixture at a temperature below that at which nucleation has commenced; and

(d) isolating the crystalline solid so deposited.

Suitable solvent systems in which solvate formation is repressed include weakly polar solvents, for example aromatic hydrocarbons such as toluene, halogeno-(1-6C)alkanes such as 1,2-dichloroethane and aliphatic di-(1-6C)alkyl ethers or (4-7C)cyclic ethers such as tetrahydrofuran, more polar protic solvents, for example (1-6C)alcohols such as ethanol and isopropanol, and polar non-protic solvents such as aliphatic esters such as ethyl acetate, aliphatic (3-6C)ketones such as acetone and aliphatic amides such as N,N-dimethylformamide. Mixtures of such solvents may also be employed such as a mixture

of toluene and isopropanol where, for example, the ratio by volume of toluene to isopropanol conveniently lies within the range 5:1 to 0.2:1, more conveniently in the range 2:1 to 0.5:1.

The solution of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline may be removed from the heat source and allowed to cool to ambient temperature or it may be cooled further, for example to about 0°C in an bath of ice and water. Alternatively, the solution may be cooled at a controlled rate to about 0°C. A suitable cooling rate is, for example, about 10°C per hour. The crystalline solid so obtained may be isolated by any conventional method, for example by filtration or centrifugation.

Conveniently, the solution of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline may be removed from the heat source and allowed to cool to about 30°C. The mixture may be reheated to about 50°C. The mixture may then be allowed to cool to ambient temperature or it may be cooled further, for example to about 0°C in a bath of ice and water. Alternatively, the solution may be cooled from about 50°C at a controlled rate to about 0°C. A suitable cooling rate is, for example, about 10°C per hour. The crystalline solid so obtained may be isolated by any conventional method, for example by filtration or centrifugation.

It will be appreciated by the man skilled in the art that the procedures described above may be varied using routine skill and knowledge. For example, provided that Form 1 ZD1839 polymorph is obtained substantially free of any other ZD1839 polymorph or any ZD1839 solvate, any of the quantity of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline that is treated, the nature and volume of the solvent and any co-solvent, the ratio of the component solvents if a solvent mixture is employed and the temperatures of the dissolution and cooling phases may be varied.

The invention is illustrated hereinafter by means of the following Examples, data and Figures in which :-

(i) X-ray diffraction patterns were obtained using a Siemens D5000 machine in $\theta$ - $\theta$ configuration over the scan range 2° 2$\theta$ to 40° 2$\theta$ with 4 seconds exposure per 0.02° 2$\theta$ increment. The X-rays were generated by a copper long-fine focus tube operated at 40kV and 40mA. The wavelength of the X-rays was 1.5406 Å. The examinations were carried out in Bragg-Brentano configuration whereby the X-ray beam was passed through an Automatic Variable Divergence Slit at V20. The sample was prepared by gently breaking up crystal

aggregates using an agate pestle and mortar. The sample was filled into a standard holder (having a flat lip) and compressed flush to the lip with a glass microscope slide. The sample was spun at 30 revolutions per minute (rpm) to improve counting statistics. The reflections are quoted as their centroid values (calculated by a computer package such as DIFFRAC/AT). It should be realised that analysis of samples with grains above 30 microns in size and non-unitary aspect ratios may affect the relative intensity of peaks. The skilled person will also realise that the position of reflections is affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence the diffraction pattern data presented are not to be taken as absolute values.

(ii) Melting points and TGA were determined using Perkin Elmer Pyris 1 DSC/TGA equipment. The pan type was aluminium (50µl size) with a pierced lid. The sample weight was approximately 1 to 4 mg. The procedure was carried out under a flow of nitrogen gas (100 ml/min) and the temperature range studied was 40°C to 300°C at a constant rate of temperature increase of 10°C per minute. The skilled person will realise that the precise value of the melting-point will be influenced by the purity of the compound, the sample weight, the heating rate and the particle size. It will therefore be appreciated that alternative readings of melting point may be given by other types of equipment or by using conditions different to those described. For the TGA, each sample (approximately 2 mg) was heated in an open ceramic crucible from 15°C to 300°C at a rate of 10°C per minute.

(iii) DRIFT spectroscopy was recorded on a Nicolet 20SXC spectrometer using a 2% w/w dispersion of the sample in powdered potassium bromide over the frequency range 4000 to 400$cm^{-1}$.

Figure 1 shows the X-ray powder diffraction pattern for Form 1 ZD1839 polymorph with the 2θ values plotted on the horizontal axis and the relative line intensity (Count) plotted on the vertical axis.

Figure 2 shows the DSC thermogram and TGA trace for Form 1 ZD1839 polymorph with temperature (°C) plotted on the horizontal axis and endothermic heat flow (milliWatts (mW)) and sample weight (percentage of initial weight) plotted on the two vertical axes.

Figure 3 shows the DRIFT spectrum for Form 1 ZD1839 polymorph with the frequency range 4000 to 400cm$^{-1}$ plotted on the horizontal axis and absorbance plotted on the vertical axis.

Figure 4 shows the X-ray powder diffraction pattern for Form 2 ZD1839 MeOH solvate with the 2θ values plotted on the horizontal axis against an expanded scale of relative line intensity values (Count) plotted on the vertical axis.

Figure 5 shows the DSC thermogram and TGA trace for Form 2 ZD1839 MeOH solvate with temperature (°C) plotted on the horizontal axis and endothermic heat flow (mW) and sample weight (percentage of initial weight) plotted on the two vertical axes.

Figure 6 shows the DRIFT spectrum for Form 2 ZD1839 MeOH solvate.

Figure 7 shows the X-ray powder diffraction pattern for Form 3 ZD1839 DMSO solvate with the 2θ values plotted on the horizontal axis against relative line intensity values (Count) plotted on the vertical axis.

Figure 8 shows the DSC thermogram and TGA trace for Form 3 ZD1839 DMSO solvate with temperature (°C) plotted on the horizontal axis and endothermic heat flow (mW) and sample weight (percentage of initial weight) plotted on the two vertical axes.

Figure 9 shows the DRIFT spectrum for Form 3 ZD1839 DMSO solvate.

**Example 1** **Form 3 ZD1839 DMSO solvate**

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline mono-solvate with dimethyl sulphoxide

With warming to about 75°C, 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (204 kg) was dissolved in a mixture of ethyl acetate (1021 litres) and dimethyl sulphoxide (181 litres) containing diatomaceous earth filter aid (5 kg). The resultant mixture was filtered and ethyl acetate (78 litres) was used to wash the filter aid solid. The filtrate and washings were combined and cooled initially to about 10°C. The mixture was then heated to about 40°C for 1 hour. The warm mixture was cooled to 0°C at a rate of about 10°C per hour. The resultant solid was collected by filtration. There was thus obtained Form 3 ZD1839 DMSO solvate as shown by XRPD and DSC analysis.

The 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline used as a starting material is disclosed in International Patent Application WO 96/33980 within Examples 1 and 10. The material may also be obtained as described in Example 4 hereinafter.

**Example 2** **Form 2 ZD1839 MeOH solvate**

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline mono-methanolate

A mixture of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (25 g) and methanol (250 ml) was stirred and heated to reflux for 30 minutes to ensure that the solid was fully in solution. The solution was cooled down at a rate of about 10°C per hour from the reflux temperature to a temperature of 0°C and then held at 0°C for 1 hour. The resultant crystalline solid was collected by suction filtration and pulled dry on the filter. There was thus obtained Form 2 ZD1839 MeOH solvate as shown by XRPD and DSC analysis.

**Example 3** **Process of conversion of Form 3 ZD1839 DMSO solvate to Form 1 ZD1839 polymorph**

Form 3 ZD1839 DMSO solvate (from Example 1) was washed with ethyl acetate (581 litres). The washed solid was mixed with ethyl acetate (895 litres) and the resultant slurry was stirred and heated to 34°C for about 1 hour. The mixture was then cooled to 0°C and held at that temperature for 2 hours to allow crystallisation to proceed. The resultant solid

was separated by filtration, washed with ethyl acetate (580 litres) and dried in a flow of warm nitrogen gas (60°C). There was thus obtained Form 1 ZD1839 polymorph (161 kg) as shown by XRPD and DSC analysis.

Example 4 Form 1 ZD1839 polymorph

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline

Whilst maintaining the temperature of the reaction mixture at about 50°C, phosphorus oxychloride (365 kg) was added to a stirred slurry of 7-methoxy-6-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/04102 within Example 25; 220 kg), triethylamine (105 kg) and toluene (1790 litres). The resultant mixture was stirred at about 50°C for 5 hours to complete the formation of 4-chloro-7-methoxy-6-(3-morpholinopropoxy)quinazoline.

The resultant stirred slurry was cooled to about 0°C and isopropanol (527 litres) was added whilst the temperature of the reaction mixture was maintained between 0° and 5°C. The reaction mass was then warmed to about 20°C and held at that temperature for about 1 hour. A solution of 3-chloro-4-fluoroaniline (168 kg) in isopropanol (228 litres) was added and the resultant reaction mixture was stirred and warmed to about 66°C and held at that temperature for about 1 hour. The mixture was stirred and cooled to about 30°C and isopropanol (662 litres) and water (1486 litres) were added in turn. A mixture of aqueous sodium hydroxide liquor (47%w/w, 755 kg) and water (40 litres) was added portionwise to the stirred reaction mixture. The resultant mixture was warmed to about 64°C and the two liquid phases were allowed to separate. The lower aqueous layer was run off. The remaining organic phase was initially cooled to about 30°C, warmed to about 50°C and finally cooled to about 20°C at a rate of about 10°C per hour. The resultant solid was collected by filtration, washed in turn with isopropanol and ethyl acetate and dried with warm nitrogen gas (60°C). There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in the form of Form 1 ZD1839 polymorph (224 kg) as shown by XRPD and DSC analysis.

Example 5 Single Crystal X-Ray Data

Well-shaped single crystals of Form 1 ZD1839 polymorph were obtained by slow evaporation at ambient temperature of a solution of the compound of the Formula I in absolute ethanol. In order to preclude the influence of air during the data collection, the selected single

crystal was protected with glue. The X-ray diffraction intensities were collected at 200°K using graphite monochromatised MoK(α) radiation and a double-pass method on a Kappa Charged Coupled Device (CCD) single-crystal X-ray diffractometer equipped with a κ-axis goniometer and an image CCD area detector (Nonius BV; Kappa-CCD Server Software, Nonius, Delft, The Netherlands). The diffraction raw data were processed using the *Denzo-SMN* (Small Molecule Nonius) computer program package, (Z Otwinowski & W Minor, Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods in Enzymology, 1997, 276, 302-326) converting the information from the digital image frame to a computer file containing h, k and l indices, background and Lp corrected intensities of the diffraction spots and estimate of errors. In order to cover the diffraction spots (reflections) within the Ewald sphere, 478 image frames were recorded with a crystal-camera distance of 35 mm with a step interval of 1°. Each frame was irradiated twice in order to discriminate the spare spots generated by cosmic radiation. Accurate unit-cell dimensions were obtained as a result of the real-space vector search that indexed reflections. Three linearly independent vectors with minimal determinant (unit-cell volume) were used to define the cell parameters within the *Denzo-SMN* package. The structure was solved with direct methods using the *SIR92* computer program package for the automatic solution of crystal structures from X-ray diffraction data (A Altomare, *et al.*, 1992) and refined with full-matrix least-squares technique. The refinements were based on F, exploiting the programs within the *MaXus* software package (S MacKay *et al.*, 1997 via the Chemistry Department, Glasgow University, Scotland; a computer program for solving, refining and publishing crystal structures from X-ray diffraction data; developed for Mac Science Co., Japan and Nonius, The Netherlands) and the *Platon* software package (A Spek *et al.*, 1992, a computer program developed for the generation and analysis of stereochemical and molecular geometry data). In the final step of the refinement calculations, all non-hydrogen atoms were allotted with anisotropic thermal displacement factors. The hydrogen atom positions were calculated geometrically and fixed at relevant positions, 0.96Å from the parent atom. The isotropic displacement factors of all hydrogen atoms were fixed to 0.05Å$^2$. In the full-matrix least squares refinements 281variables were refined against 3184 reflections (with $F^2_o > 3\sigma F^2_o$). Further, the final reliability values converged to R = 0.0404 and Rw = 0.0440. Relevant crystal data together with experimental details and structural refinement parameters are summarised in Table A:1 and atomic coordinates are provided in Table A:2.

**Table A:1.** Experimental and Refinement Calculation data for Form 1 ZD1839 polymorph

| | |
|---|---|
| *Crystal data* | |
| $C_{22}H_{24}ClFO_3N_4$ | MoK(α) radiation: |
| $M_r = 446.91$ | λ = 0.71073 Å |
| Crystal System: Triclinic | Space group: P-1 |
| Unit-cell parameters: | average values from image indexed reflections |
| a = 8.876(1) Å | α = 93.51(1)° |
| b = 9.692(1) Å | β = 97.36(1)° |
| c = 12.543(1) Å | γ = 101.70(1)° |
| V = 1043.6(2) $Å^3$ | crystal shape: needle |
| Z = 2 | 0.14 x 0.14 x 0.29 mm |
| $D_x$ = 1.4222(3) Mg m-3 | colourless |
| T = 200K | μ = 2.2 cm-1 |
| hkl-range: | -10 < h < 11, -9 < k < 12, -16< l < 16 |
| F(000) = 468.0 electrons | |
| *Data collection* | |
| Nonius BV KappaCCD Diffractometer | |
| Number of collected frames: | 478 |
| Number of repeats: | 1 |
| Distance: crystal-detector | $D_x$ = 35 mm |
| Phi-rotation step | 1 |
| Exposure time: | 15 sec / frame |
| Resolution: | 0.66 Å |
| Covered θ-range: | 1 – 27.5 |
| Total number of measured reflections: | 4646 |
| Number of unique observed reflections, $F^2_o > 3\sigma(F^2_o)$ : | 3184 |
| Absorption correction: | none |
| Extinction parameter (Zachariasen, 1970) | 9.9479 exp –3 |
| *Refinement* | |
| MaXus (1997) | $(\Delta/\sigma)_{max}$ = 0.0006 |
| Refinement on F | $(\Delta/\sigma)_{mean}$ = 0.0001 |
| R = 0.0404 | $\Delta\rho_{max}$ = 0.21 e $Å^{-3}$ |
| Rw = 0.0440 | $\Delta\rho_{min}$ = -0.22 e$Å^{-3}$ |
| Weighting scheme: | $w = 1/(\sigma^2 F_o^2 + (0.0300)F^2)$ |
| Atomic scattering factors: | maXus (1997) |
| 281 parameters | |
| Atomic displacement factors: | |
| *non*-H atoms | anisotropic |
| H atoms | $U_{(iso)}$=0.05 $Å^2$ |

**Table A:2.** Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for Form 1 ZD1839 polymorph.

| Atom | x | y | z | U(*eqv*) [Å$^2$] |
|---|---|---|---|---|
| Cl(19) | 0.36275(4) | 0.84068(3) | 0.42511(2) | 0.0619(1) |
| F18 | 0.39031(7) | 1.08739(6) | 0.29892(5) | 0.0549(2) |
| O20 | 0.93090(8) | 0.14285(6) | -0.02633(5) | 0.0390(2) |
| O22 | 0.86297(7) | 0.20079(6) | 0.16029(4) | 0.0340(2) |
| O29 | 1.25684(7) | 0.45236(6) | 0.64985(4) | 0.0370(2) |
| N1 | 0.75916(9) | 0.54835(8) | -0.16301(6) | 0.0373(3) |
| N3 | 0.65090(9) | 0.69616(7) | -0.04568(6) | 0.0351(3) |
| N11 | 0.62866(9) | 0.64913(7) | 0.13265(5) | 0.0319(3) |
| N26 | 1.09809(9) | 0.28952(7) | 0.45555(5) | 0.0307(3) |
| C2 | 0.69633(12) | 0.65563(10) | -0.13936(7) | 0.0395(3) |
| C4 | 0.67182(10) | 0.61580(8) | 0.03459(7) | 0.0285(3) |
| C5 | 0.73888(10) | 0.49402(8) | 0.02221(6) | 0.0271(3) |
| C6 | 0.76526(10) | 0.40484(8) | 0.10497(7) | 0.0291(3) |
| C7 | 0.83115(10) | 0.29184(8) | 0.08601(7) | 0.0283(3) |
| C8 | 0.87139(10) | 0.26072(9) | -0.01814(7) | 0.0293(3) |
| C9 | 0.84831(10) | 0.34655(9) | -0.09798(7) | 0.0312(3) |
| C10 | 0.78163(10) | 0.46535(8) | -0.07936(7) | 0.0289(3) |
| C12 | 0.56635(10) | 0.76385(8) | 0.16763(7) | 0.0295(3) |
| C13 | 0.56934(11) | 0.88739(9) | 0.11619(7) | 0.0355(3) |
| C14 | 0.50760(12) | 0.99477(9) | 0.15990(7) | 0.0383(3) |
| C15 | 0.44717(11) | 0.98025(9) | 0.25485(8) | 0.0367(3) |
| C16 | 0.44402(11) | 0.85905(9) | 0.30697(7) | 0.0350(3) |
| C17 | 0.50256(11) | 0.75092(9) | 0.26345(7) | 0.0327(3) |
| C21 | 0.97517(12) | 0.10326(10) | -0.12755(7) | 0.0414(3) |
| C23 | 0.83007(11) | 0.23029(9) | 0.26738(7) | 0.0323(3) |
| C24 | 0.88933(11) | 0.12432(9) | 0.33581(7) | 0.0346(3) |
| C25 | 1.06324(12) | 0.16967(9) | 0.37237(7) | 0.0374(3) |
| C27 | 1.25450(12) | 0.37519(10) | 0.46087(7) | 0.0411(3) |
| C28 | 1.28014(12) | 0.49842(10) | 0.54589(8) | 0.0426(4) |
| C30 | 1.10343(12) | 0.36784(10) | 0.64376(7) | 0.0413(3) |
| C31 | 1.07840(11) | 0.24200(10) | 0.56203(7) | 0.0381(3) |

Temperature factor of the form : T = exp[-2$\pi^2$U], U= U(*eqv*) where
U(*eqv*) =1/3 Σ(*i*)Σ(*j*){U(*ij*)*a*(*i*)*a*(*j*)a(*i*)a(*j*)

**Example 6** **Tablets**

Specific examples of tablet formulations of an active substance of the invention comprising Form 3 ZD1839 DMSO solvate, Form 2 ZD1839 MeOH solvate or Form 1 ZD1839 polymorph, are described hereinafter.

**100 mg Tablet**

| **Core:** | **mg/tablet** |
|---|---|
| active substance | 100 |
| Lactose | 65.4 |
| Microcrystalline Cellulose | 20 |
| Croscarmellose Sodium | 8 |
| Polyvidone | 4 |
| Sodium Lauryl Sulphate | 0.6 |
| Magnesium Stearate | 2 |
| **Coating:** | **mg/tablet** |
| Methylhydroxypropylcellulose | 3 |
| Polyethylene Glycol, PEG 300 | 0.6 |
| Titanium Dioxide | 0.2 |

**250 mg Tablet**

| **Core** | **mg/tablet** |
|---|---|
| active substance | 250 |
| Calcium Hydrogen Phosphate | 163.5 |
| Microcrystalline Cellulose | 50 |
| Croscarmellose Sodium | 20 |
| Polyvidone | 10 |
| Sodium Lauryl Sulphate | 1.5 |
| Magnesium Stearate | 5 |
| **Coating:** | **mg/tablet** |
| Methylhydroxypropylcellulose | 7.6 |
| Polyethylene Glycol, PEG 300 | 1.5 |
| Titanium Dioxide | 0.5 |

## CLAIMS

1. A crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate.

2. The solvate according to claim 1 characterised by an X-ray diffraction pattern having characterising peaks at about 8.9, 17.8, 22.6 and 23.2° on the 2θ scale.

3. The solvate according to claim 1 characterised by an X-ray diffraction pattern substantially as shown in Figure 7.

4. The solvate according to claim 1 characterised by a decomposition point in the range of about 127°C to 132°C.

5. The solvate according to claim 1 characterised by one or both of the Differential Scanning Calorimetry thermogram and Thermal Gravimetric Analysis trace substantially as shown in Figure 8.

6. The solvate according to claim 1 characterised by a Diffuse Reflectance Infrared Fourier Transform spectrum with distinguishing peaks at about 1640, 1520, 1450, 880 and 560$cm^{-1}$.

7. The solvate according to claim 1 characterised by a Diffuse Reflectance Infrared Fourier Transform spectrum substantially as shown in Figure 9.

8. A crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate according to claim 1 which is substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph.

9. A process for preparing a crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate according to claim 1 which comprises :-

(a) heating a mixture of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in dimethyl sulphoxide or a solvent mixture containing dimethyl sulphoxide and a co-solvent until dissolution has occurred;

(b) reducing the temperature of the solvent system to induce spontaneous nucleation;

(c) maintaining the mixture at a temperature below that at which nucleation has commenced; and

(d) isolating the crystalline solid so deposited.

10. A crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate.

11. The solvate according to claim 10 characterised by an X-ray diffraction pattern having characterising peaks at about 6.5, 10.0 and 13.2° on the 2θ scale.

12. The solvate according to claim 10 characterised by an X-ray diffraction pattern substantially as shown in Figure 4.

13. The solvate according to claim 10 characterised by a decomposition point in the range of about 125°C to 130°C.

14. The solvate according to claim 10 characterised by one or both of the Differential Scanning Calorimetry thermogram and Thermal Gravimetric Analysis trace substantially as shown in Figure 5.

15. The solvate according to claim 10 characterised by a Diffuse Reflectance Infrared Fourier Transform spectrum with distinguishing peaks at about 3380, 1650, 1530, 1450, 1235, 870 and 570$cm^{-1}$.

16. The solvate according to claim 10 characterised by a Diffuse Reflectance Infrared Fourier Transform spectrum substantially as shown in Figure 6.

17. A crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate according to claim 10 which is substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph.

18. A process for preparing a crystalline form of the compound of the Formula I substantially in the form of Form 2 ZD1839 MeOH solvate according to claim 10 which comprises :-

(a) heating a mixture of the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline in methanol or a solvent mixture containing methanol and a co-solvent until dissolution has occurred;

(b) reducing the temperature of the solvent system to induce spontaneous nucleation;

(c) maintaining the mixture at a temperature below that at which nucleation has commenced; and

(d) isolating the crystalline solid so deposited.

19. A process for the preparation of the compound of Formula I substantially in the form of Form 1 ZD1839 polymorph which comprises :-

(a) washing Form 3 ZD1839 DMSO solvate according to claim 1 with a solvent or solvent mixture substantially to remove dimethyl sulphoxide; and

(b) isolating the Form 1 ZD1839 polymorph so formed.

20. A process for the preparation of the compound of Formula I substantially in the form of Form 1 ZD1839 polymorph which comprises :-

(a) washing Form 2 ZD1839 MeOH solvate according to claim 10 with a solvent or solvent mixture substantially to remove methanol; and

(b) isolating the Form 1 ZD1839 polymorph so formed.

22. A pharmaceutical composition which comprises the crystalline form of the compound of the Formula I according to claim 1 or 10 and a pharmaceutically-acceptable diluent or carrier.

23. A pharmaceutical composition according to claim 22 that is adapted for oral administration.

**Figure 1**

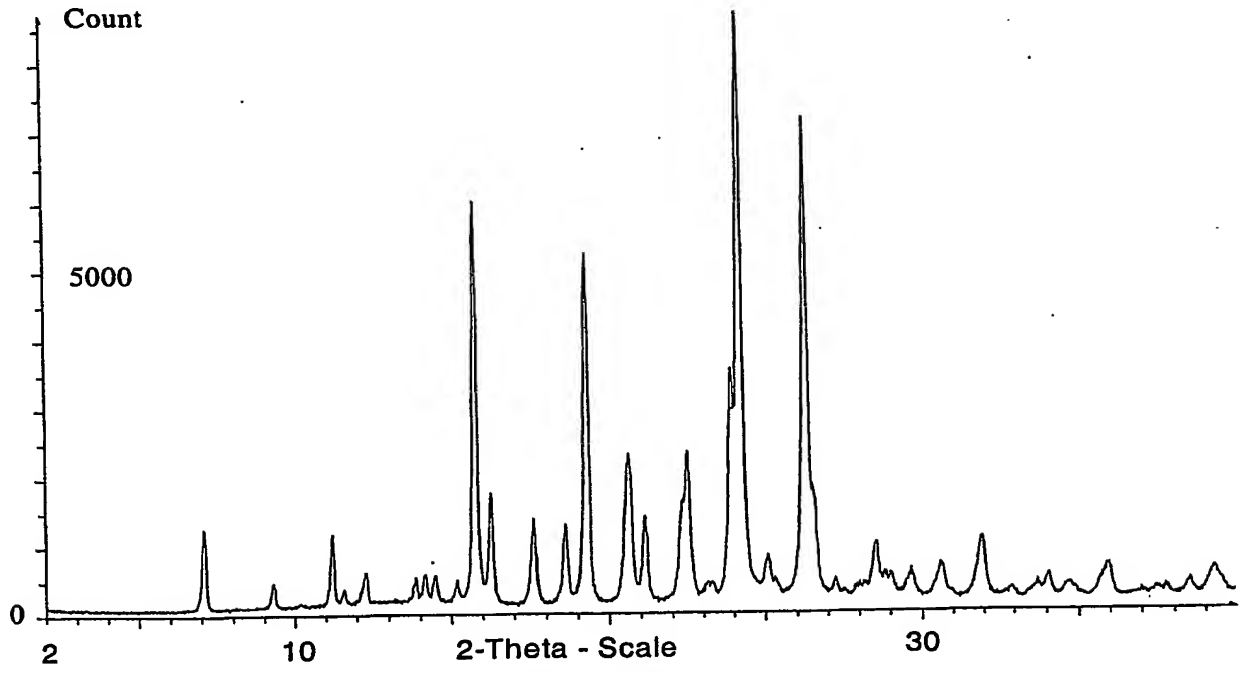



FIG 1/9 XRPD Pattern of Form 1 ZD1839 Polymorph

**Figure 2**

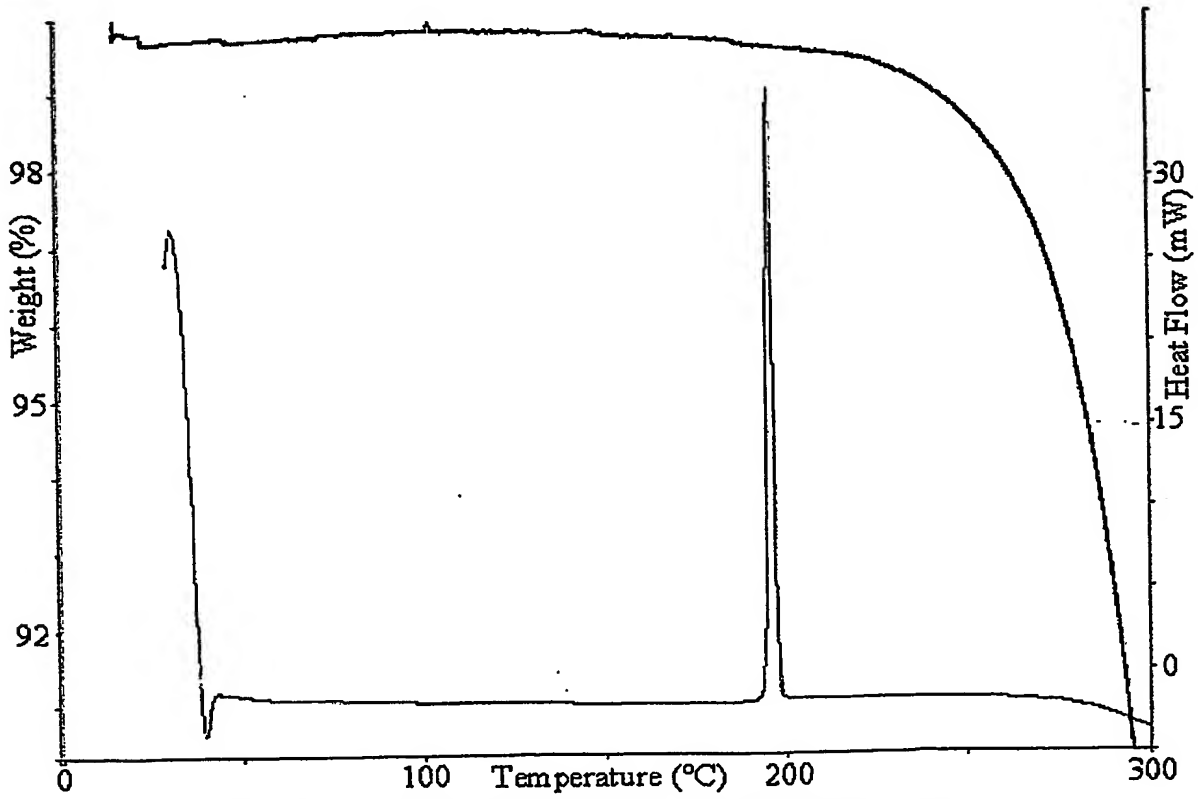



FIG 2/9 DSC & TGA scans for Form 1 ZD1839 Polymorph

**Figure 3**

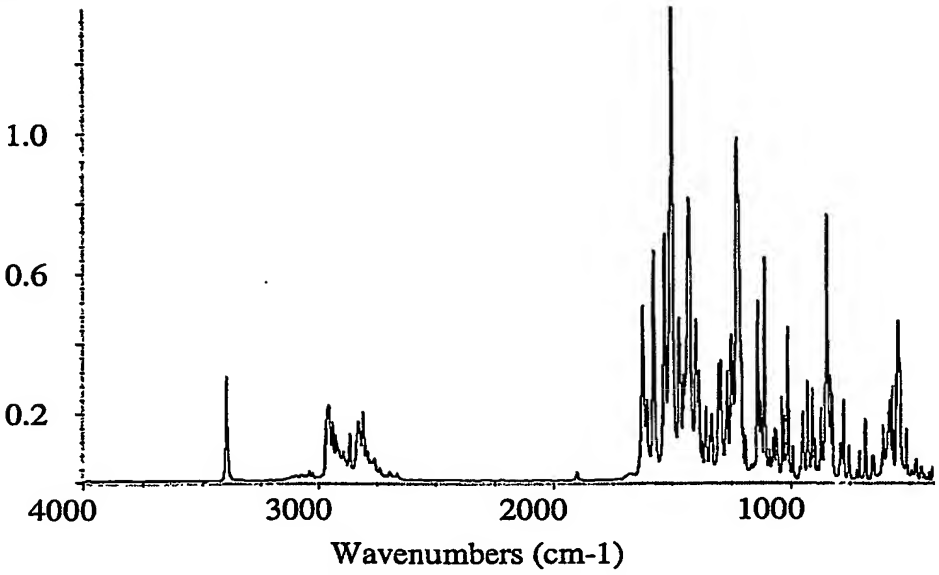



FIG 3/9 DRIFT scan for Form 1 ZD1839 Polymorph

**Figure 4**

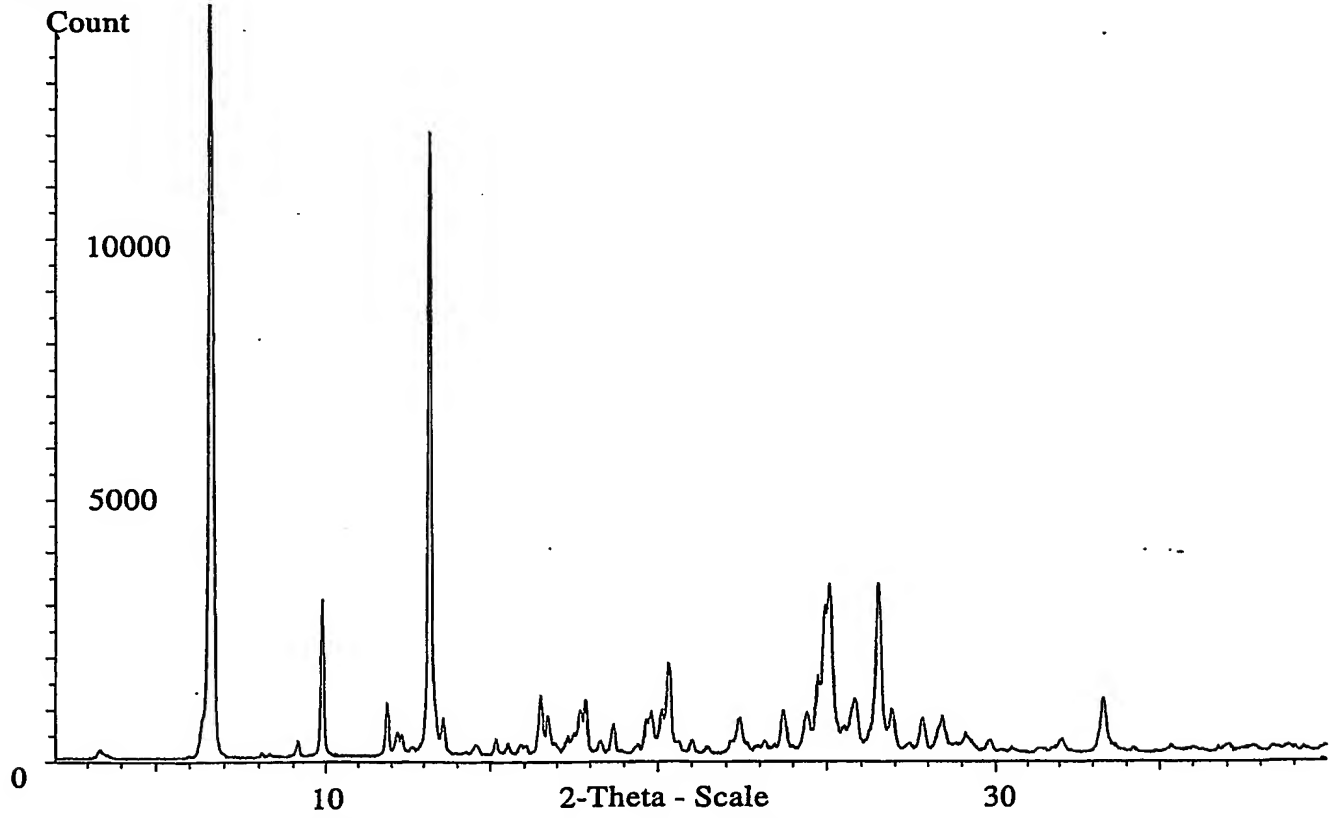



FIG 4/9 XRPD Pattern of Form 2 ZD1839 MeOH solvate

**Figure 5**

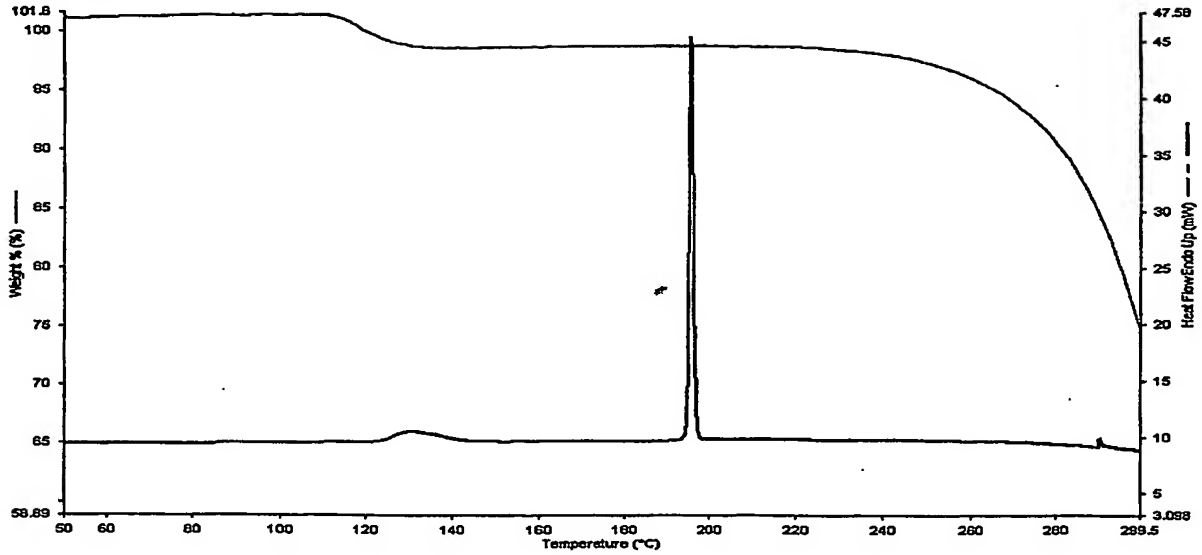



FIG 5/9 DSC & TGA scans for Form 2 ZD1839 MeOH solvate

**Figure 6**

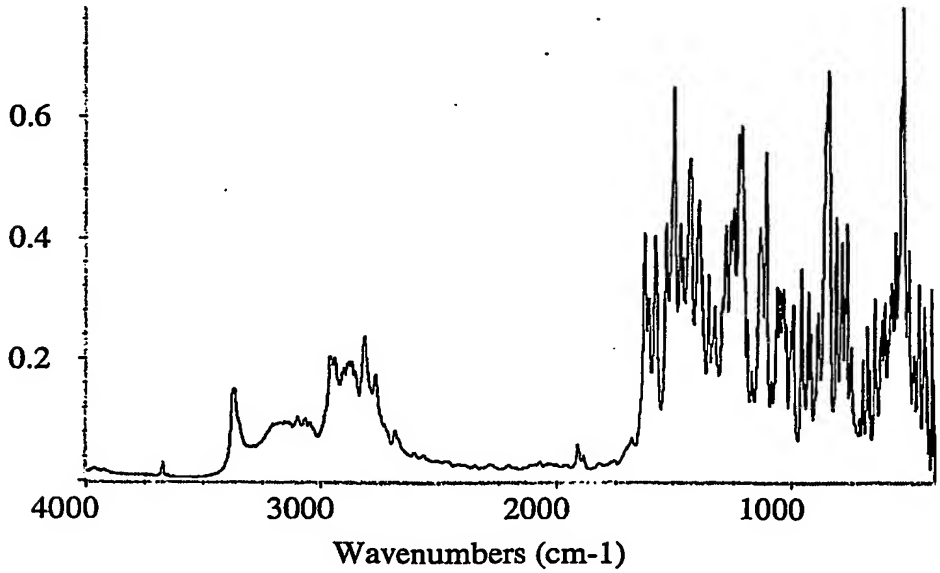



FIG 6/9 DRIFT scan for Form 2 ZD1839 MeOH solvate

**Figure 7**

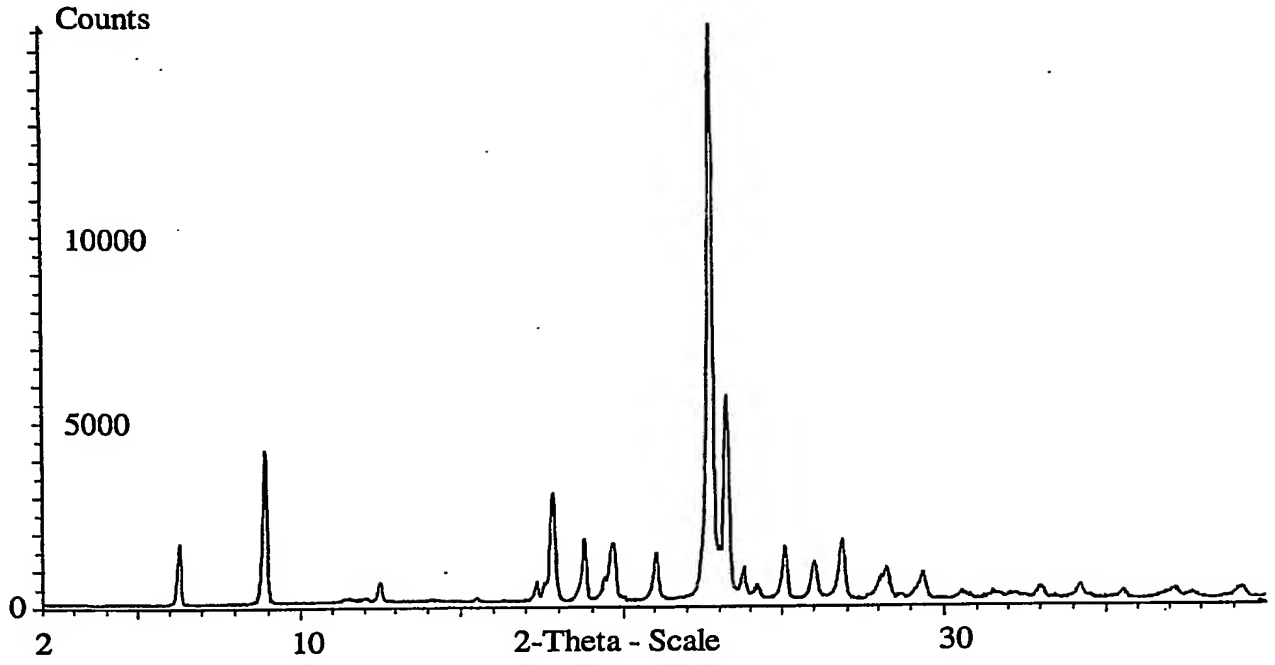



FIG 7/9 XRPD Pattern of Form 3 ZD1839 DMSO solvate

**Figure 8**

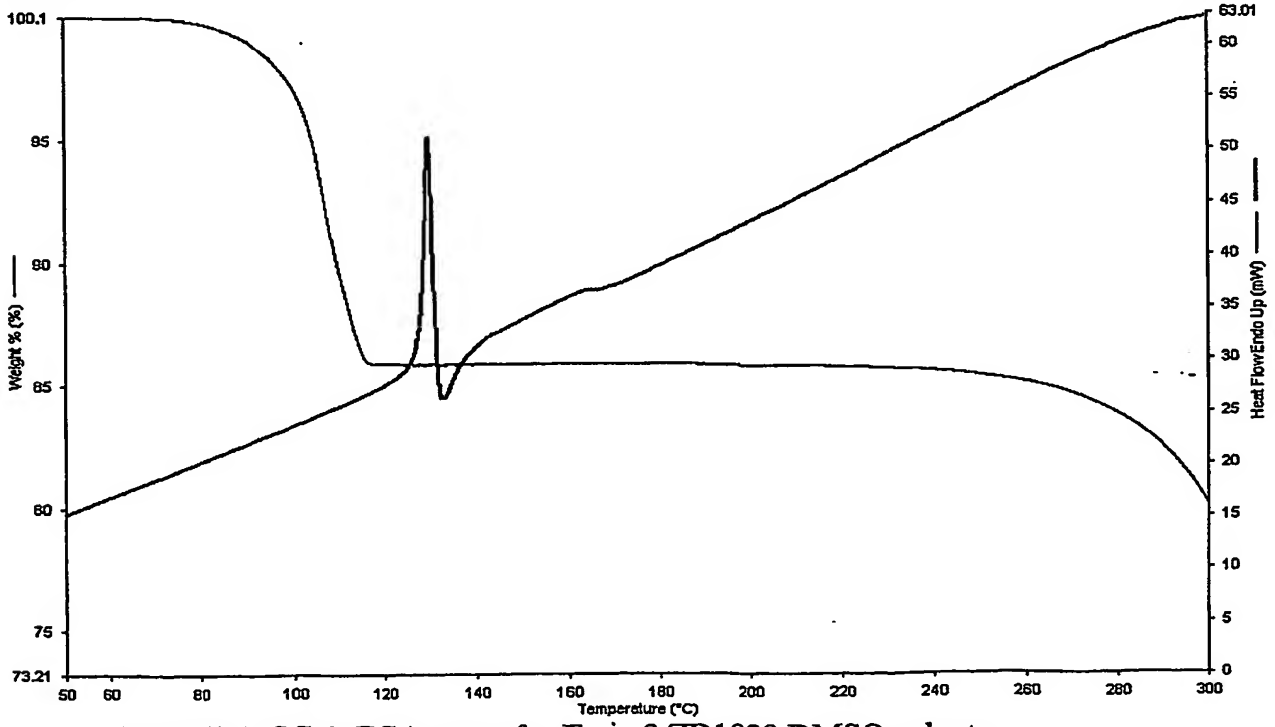



FIG 8/9 DSC & TGA scans for Form 3 ZD1839 DMSO solvate

**Figure 9**

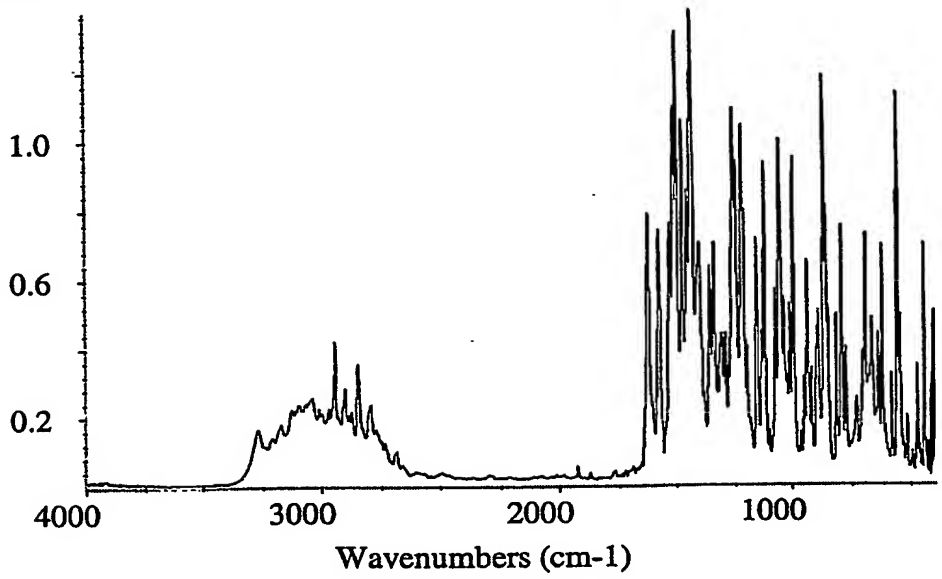



FIG 9/9 DRIFT scan for Form 3 ZD1839 DMSO solvate